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A different yet traditional approach to neoadjuvant treatment of breast cancer: The combination of epirubicin and docetaxel

Neoadjuvant epirubicin docetaxel in breast cancer'

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Abstract
Aim: Epirubicin-docetaxel (ET) combination is an unusual and less frequently recommended regimen in the neoadjuvant treatment of breast cancer. In this study, we aimed to evaluate the efficacy of this combination.
Material and Methods: The study involved 46 women diagnosed with breast cancer in 2009-2019 who received neoadjuvant therapy. All received epirubicin 80 mg/m2 and docetaxel 75 mg/m2 (on day-1) over a 21-day period, in varying cycles.
Results: The mean age of the patients was 49.3 ± 12.3 years. Twenty-one (45.7%) were premenopausal and 25 (54.3%) postmenopausal, 27 (64.3%) were ≤T2 at the time of diagnosis and 15 (35.7%) were >T2. Clinical involvement of the lymph nodes was present in 36 (80%). Eleven (28.9%) were luminal-A, 20 (52.6%) luminal-B, 2 (5.3%) HER2-positive, and 5 (13.2) triple–negative. Twenty-six (56.5%) patients had received 3 cycles and 20 (43.5%) had more than 3. In the clinical-response evaluation, complete response was observed in 10 (21.7%) patients, partial response in 24 (52.2%), stable disease in 9 (19.6%), and progressive disease in 3 (6.5%). The objective-response rate (ORR) was 73.9%. Total pathological-complete-response (pCR) was observed in 7 (15.2%) patients. pCR rates were higher in patients without clinical-lymph-node involvement (44.4% vs 8.3%, p:0.022). The median follow-up time was 37.5 months.
Discussion: Although the combination of ET in the neoadjuvant treatment of breast cancer is not among the regimens recommended in the guidelines, according to our study, it has a significant contribution to ORR and pCR, especially in node negatives.

Keywords
Breast Cancer, Docetaxel, Epirubicin, Neoadjuvant Chemotherapy, Response

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Introduction

Breast cancer is the second most common type of cancer worldwide and one of the most common causes of cancer-related deaths in women [1]. Commencing treatment with neoadjuvant chemotherapy (NACT) in the locally advanced stage has numerous benefits. NACT obviates the need for extensive surgery to the breast and axilla by causing tumor downstaging. Thus, complications that pose a limitation on movement and lower quality of life after total mastectomy, such as lymphedema, are prevented [2]. It is also easier to evaluate the tumor response to systemic therapy with NACT. However, the failure to achieve a complete pathological response with NACT is an important prognostic factor for the risk of recurrence, particularly in the triple-negative and HER2-positive subgroups. At the same time, although there has been shown to be little difference between NACT and adjuvant chemotherapy in terms of overall survival, early initiation of systemic therapy also contributes to early eradication of micrometastases and a decrease in the risk of recurrence [3,4].

Anthracycline and taxane-based chemotherapies are primarily employed in neoadjuvant therapy. The generally recommended treatment in HER2-negative patients is a dose-dense anthracycline (epirubicin or doxorubicin) and cyclophosphamide combination, followed by taxane-based regimens alone (paclitaxel or docetaxel), requiring a total six-month treatment period [5]. The combination of epirubicin and docetaxel (ET) is applied for six cycles at three-week periods and requires a total length of treatment of four months. The ET regimen is not included among the primary options in neoadjuvant therapy in the National Comprehensive Cancer Network (NCCN) guideline. However, due to its tolerability, the regimen can be used in selected patients.

The purpose of this study was to determine the effectiveness of an ET combination in neoadjuvant therapy, to analyze the factors affecting the clinical and pathological response, and to improve our approach to identifying candidates for NACT.

Material and Methods

One hundred twenty-seven patients were diagnosed with breast cancer and received NACT in our center between December 2009 and December 2019. Only 46 patients receiving the ET regimen out of these 127 patients were included in the study. All patients were diagnosed through biopsy, and their post-NACT pathologies were reported in our center. The patients' clinical, demographic, and pathological characteristics, treatment choices, responses to treatment, and survival/mortality were analyzed retrospectively from the hospital's data-processing records. Ethical approval for the study was received from Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee on 21.1.2020 (document number: 24237859-171, approval number: 2019/374).

Patients diagnosed with pathological breast cancer and scheduled for NACT initially underwent mammography and/or magnetic resonance imaging. Lymph node involvement at the time of diagnosis was evaluated with lymph node biopsy if no radiological consensus was achieved. Thoracic-abdominal computed tomography, bone scintigraphy, or PET-computed tomography were performed to screen for distant metastasis. NACT was performed with intravenous administration of epirubicin 80 mg/m2 and docetaxel 75 mg/m2 on day 1 at varying cycles over 21-day periods. Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) rules were used in the evaluation of clinical responses, and patients were divided into four groups accordingly, complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Pathological response evaluation was carried out by our center's pathology department. Patients with no tumor cells observed in the breast and axilla were regarded as exhibiting pathological complete response (pCR). Patients were also examined separately in terms of pathological responses for the breast and axilla.

The immunohistochemical method was employed to determine molecular subtypes (luminal A, luminal B, HER2-positive, and triple-negative). Patients were divided into subtypes through the investigation of estrogen receptor (ER), progesterone receptor (PR), HER2, and Ki-67 percentages. Patients who were ER-positive (ER+), with PR ≥20%, HER2-negative, and with Ki67 <10% were regarded as Luminal A. Luminal B cases were defined as ER+, HER2-negative, and with one of Ki67 ≥20% or PR negative <20%, or ER+, HER2-positive, with any Ki67 level and any PR level. HER2+ (non-luminal) tumors were defined as HER2+ and ER- and PR-negative. Triple-negative tumors were defined as ER-, PR-, and HER2-negative.

Statistical analysis

Statistical analysis was performed on SPSS 23.0 software. Descriptive statistics were expressed as numbers and percentages for categorical variables and as mean, median, standard deviation, minimum, and maximum for numerical variables. The One Sample Kolmogorov-Smirnov test was applied to determine the normality of distribution in the groups. Differences in categorical variable rates between independent groups were evaluated using the chi-square test. Alpha significance was set at $p<0.05$.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

The patients' general characteristics are summarized in Table 1. Their mean age was 49.3 ± 12.3 years (min. 31, max. 74). All were women; 21 (45.7%) of the 46 patients were premenopausal and 25 (54.3%) postmenopausal. Twenty-seven (64.3%) of the 42 patients whose T stages were known at the time of diagnosis were ≤T2 and 15 were (35.7%) >T2. Lymph node involvement was present in 36 (80%) of the 45 patients whose lymph node status was known at the time of diagnosis, but not in the remaining nine (20%). Eleven (28.9%) of the 38 patients whose immunohistochemistry (IHC) records were available at the time of diagnosis were luminal A, 20 (52.6%) were luminal B, two (5.3%) were HER2-positive, and five (13.2%) were triple-negative. Twenty-six (56.5%) of the entire patient group had received three cycles of ET and 20 (43.5%) more than three. Subtype alteration after neoadjuvant ET was present in four (12.5%) of the 32 patients with residual tumors whose records were available, while no change was present in 28 (87.5%). The median length of follow-up was 37.5 months (min. 13 max. 142).

Clinical response and pathological response rates are summarized in Table 2. Clinical response evaluation revealed CR in 10 (21.7%) patients, PR in 24 (52.2%), SD in nine (19.6%), and PD in three (6.5%). The objective response rate (ORR) was 73.9%. No significant differences in clinical response rates were observed in terms of menopause status, T stage at the time of diagnosis, presence or absence of clinical lymph node involvement at the time of diagnosis, Ki-67 index, and receipt of three or more cycles of ET.

Pathological response analysis revealed pCR in seven (15.2%) patients (Table 2). Pathological responses were evaluated in the breast and axilla together (Table 3). Total pathological response rates in the breast and axilla together were higher in patients without clinical lymph node involvement than in those with such involvement (44.4% vs 8.3%, respectively p:0.022). No significant difference in total pathological complete response rates was observed in terms of menopausal status, T stage at the time of diagnosis, Ki-67 index, molecular subtype, or number of ET cycles. The pCR rate in the axilla alone was higher among patients without clinical lymph node involvement than in those with such involvement (77.8% vs 22.2%, p:0.003). No Grade 3-4 toxicity was observed.

Table 1. Clinicopathological features of the patients.

Variable	Patients (%)
Age, years (min-max)	49.3 ± 12.3 (min.31-max.74)
Menopausal Status (n=46)	
Pre-menopause	21 (45.7)
Post-menopause	25 (54.3)
Histologic type (n=43)	
Ductal carcinoma	39 (90.7)
Lobular carcinoma	3 (7.0)
Papillary carcinoma	1 (2.3)
Clinical T Stage (n=42)	
T1	12 (28.6)
T2	15 (35.7)
T3	11 (26.2)
T4	4 (9.5)
Clinical Lymph Node Status (n=45)	
N+	36 (80.0)
N-	9 (20.0)
Molecular subtype (n=38)	
Luminal A	11 (28.9)
Luminal B	20 (52.6)
HER2 +	2 (5.3)
Triple -	5 (13.2)
Ki-67 index (n=29)	
≤%10	10 (34.5)
>%10 ≤%20	7 (24.1)
>%20	12 (41.4)
Operation Type (n=46)	
MRM	41 (89.1)
BCS	5 (10.9)
Number of ET cycles (n=46)	
3 cycles	26 (56.5)
4 cycles	11 (23.9)
5 cycles	2 (4.3)
6 cycles	7 (15.2)

MRM: Modified Radical Mastectomy, BCS: Breast-conserving Surgery, ET: epirubicin+docetaxel

Table 2. Response rates to neoadjuvant chemotherapy.

Response	All patients, n=46 (%)
Clinical response	
CR	10 (21.7)
PR	24 (52.2)
SD	9 (19.6)
PD	3 (6.5)
Pathological Response	
pCR (breast+axilla)	7 (15.2)

CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease, pCR: Pathological complete response

Table 3. Clinicopathological features and pathological response rates to neoadjuvant chemotherapy (evaluation of the breast and axilla together)

Variable	pCR (+)	pCR (-)	p value
Menopausal Status (n=46)			
Pre-menopausal	3 (14.3)	18 (85.7)	1.000
Post-menopausal	4 (16.0)	21 (84.0)	
Clinical T Stage (n=42)			
T1-2	4 (14.8)	23 (85.2)	0.686
T3-4	3 (20.0)	12 (80.0)	
Clinical Lymph Node Status (n=45)			
N+	3 (8.3)	33 (91.7)	0.022
N-	4 (44.4)	5 (55.6)	
Ki-67 (n=29)			
>%20	2 (16.7)	10 (83.3)	1.000
≤%20	3 (17.6)	14 (82.4)	
Molecular subtype (n=38)			
Luminal A	2 (18.2)	9 (81.8)	-----
Luminal B	3 (15.0)	17 (85.0)	
HER2 +	0 (0.0)	2 (100.0)	
Triple -	1 (20.0)	4 (80.0)	
Number of ET cycles (n=46)			
≤3	2 (7.7)	24 (92.3)	0.213
>3	5 (25.0)	15 (75.0)	

pCR: Pathological complete response, ET: epirubicin+docetaxel

Discussion

Important recent studies have shown the usefulness of NACT in operable breast cancer [3,4]. The importance of the pCR rates obtained with NACT in predicting survival particularly encourages clinicians to use neoadjuvant therapy in high-risk patients [6]. The principal advantages of neoadjuvant therapy include less extensive surgery and the fact that as a result, patients' quality of life is significantly protected [2].

The first recommended regimens for neoadjuvant therapy in HER2-negative disease in the NCCN guideline are four cycles of dose-dense anthracycline + cyclophosphamide (AC) followed by a three-month paclitaxel regimen or a four-cycle TC (docetaxel+cyclophoshamide) regimen alone [7]. The addition of trastuzumab and pertuzumab in combination with chemotherapy is recommended for HER2-positive disease [8].

The GEPARDUO study showed the superiority of a neoadjuvant AC combination followed by sequential docetaxel therapy over concurrent docetaxel therapy in achieving pCR in operable breast cancer (pCR rates 14.3% vs 7%, respectively, p<0.001).

However, the high frequency of hematological side effects in particular with the AC regimen, and the fact that these make the regimen difficult for patients to tolerate, make adherence to it problematic. The use of granulocyte colony- stimulating factor (GCSF) is required for neutropenia prophylaxis in order to prevent the postponement of treatment and a decrease in dose density due to neutropenia. In addition, due to this regimen's very high emetogenic property, it requires the use of numerous antiemetics and close follow-up to increase compliance [9]. Additionally, doxorubicin is more likely to cause cardiac toxicity than epirubicin. Due to the possibility of cumulative toxicity, patients require careful life-long cardiac follow-up [10]. The standard duration of NACT with sequential therapy is six months (or longer if dose delay is required), but only four months with the ET regimen [8,11]. Epirubicin-docetaxel combination therapy offers a number of advantages, such as easier toleration and follow-up, and a shorter duration than sequential therapy for neoadjuvant therapy. These explains its preference in fragile patients scheduled for NACT.

Previous studies have investigated the efficacy of neoadjuvant ET [6,12]. A study from Korea published in 2020 involved a retrospective evaluation of clinical and pathological responses and factors affecting them in 40 patients receiving neoadjuvant ET. An ORR of 62.5% (2.5% CR + 60% PR) was determined by clinical response analysis, while pCR was observed in 5% of patients by pathological response evaluation. The authors concluded that ET should be considered in neoadjuvant therapy in selected patients [11]. In light of the above, and based on the hypothesis that the ET regimen may be a tolerable option in neoadjuvant therapy, we decided to perform a retrospective analysis of clinical and pathological response rates among patients receiving ET in our center between December 2009 and October 2019. Forty-six of our patients received the ET regimen. These were patients indicated for NACT but whom we considered too fragile to tolerate six-month NACT. Due to the realization of the importance of NACT in recent years and the fact that standards have not yet been established in many developing centers, including our own institution, more than half of our patients received half the treatment they should have been administered. Although this study reflects real-life data, this nevertheless constitutes one of its principal limitations.

The great majority of patients were in the luminal subtype (28.9% luminal A and 52.6% luminal B) at the time of diagnosis (13.2% triple-negative, 5.3% HER2-positive). Combined regimens, including neoadjuvant trastuzumab and pertuzumab are known to be important in achieving pCR in HER2-positive breast cancer [13]. However, two of the HER2-positive patients diagnosed in 2009 in the present study had received a neoadjuvant ET regimen, and partial response was observed in both. This response, seen in a very few patients is insufficient to allow us to make any recommendation regarding neoadjuvant therapy in HER2-positive breast cancer.

Since the patients included in this study had been diagnosed until January 2019, and the importance of preoperative total neoadjuvant therapy has become better understood in recent years, the rate of completion of preoperative NACT among our patients was low. Although 15.2% of patients completed a neoadjuvant six-cycle ET regimen, analysis of clinical responses revealed an ORR of 73.9% (21.7% CR + 52.2% PR). All three (6.5%) of our patients with progression were in the luminal A group, which is known to exhibit the lowest response to neoadjuvant chemotherapy. When the breast and axilla were evaluated together, pCR was present in seven (15.2%) patients. Considering also that more than half (56.5%) of our patients received only three cycles of ET, our findings support the idea that the neoadjuvant ET regimen is not at all inferior to the AC + sequential docetaxel regimen and can be safely used in selected patients.

No clinicopathological characteristic affecting clinical response rates with ET in a statistically significant manner was identified in this study. Evaluation of the breast and axilla both separately and together in terms of pathological response revealed significantly higher pCR rates in both analyses in patients without clinical lymph node involvement (77.8% vs 22.2%, p:0.003, and 44.4% vs 8.3%, p:0.022, respectively). Considering that hematological and cardiac side effects are more controllable, the lower risk of emesis, and the shorter time elapsing to surgery, we think that the ET regimen can be safely employed in HER2-negative patients without lymph node involvement at the time of diagnosis and who are regarded as potential candidates for NACT.

Although we think that our findings are important, there are nevertheless a number of limitations in this research. Patients receiving NACT between 2009 and 2019 were included in the study. Our patient number was low, since the importance of neoadjuvant therapy has become better understood in recent years and because ET is not one of the regimens to which we attach primary consideration in neoadjuvant therapy, and their follow-up times were not particularly long. Further more extensive, prospective studies are now needed to support our findings.

Conclusion

The findings of this study show that the ET combination in the neoadjuvant treatment of breast cancer makes a significant contribution to ORR and pCR, especially in node-negative cases. Although the ET regimen is not included among the primary options in neoadjuvant therapy in the NCCN guideline, in light of the clinical and pathological response rates in this study, we concur with the idea that ET can be safely used in the treatment of HER2-negative NACT candidate patients, particularly those without clinical lymph node involvement. This research now needs to be supported by prospective studies.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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